## REMARKS

Claims 6, 10-11, 17, 20, 22, 27-29, 31-35, and 37 are pending in the subject application. Claims 1-5, 7-9, 12-16, 18-19, 21, 23-26, 30 and 36 have been canceled.

## REJECTION UNDER 35 U.S.C. § 103(a)

Claims 6-11, 17-22, 27-29, 31-35 and 37 have been rejected under 35 U.S.C.§103(a) over Gonzalez et al. (U.S. Patent 6,015,673) in view of Willhauck et al. (Biotechniques (1998) 25:656-659) and further in view of Stanta et al. (Biotechniques (1991) 11(3): 303, 306, and 308).

Applicants respectfully disagree as Gonzalez does not teach each and every element of the claimed invention and Buck does not make up for these deficiencies. For instance, the present claims involve specific oligonucleotide sequences capable of amplifying DPD mRNA from FPE tissue. Gonzalez does not teach or suggest this. The Examiner states that the SEQ ID NO: 5 of Gonzalez is "substantially identical" to one of the claimed oligonucleotides. However, there is no teaching or suggestion of the four complete claimed primer sequences. Nor is there teaching or suggestion of the necessity for nucleotide sequences to robustly provide reproducible quantitation of DPD expression in samples isolated from FPE tissue and not to simply have the ability to bind to the DPD gene.

As provided in the Declaration of Kathleen Danenberg, even though a primer may bind to the DPD gene, they do not necessarily have the ability to detect DPD expression at such low levels. The present invention provides oligonucleotide primer sequences that have been proven preferable to DPD primer sequences of a research diagnostic company. To say that all primer pairs should be expected to work fails to address the facts of the present invention that is that even among primer pairs developed in-house at RGI, as discussed in Kathleen Danenberg's Declaration, half of the primer pairs failed to detect DPD expression in tissue samples. Furthermore, even among the successful primer pairs there is a marginal degree of enhanced specificity in detection of low DPD levels of expression.

As discussed in the Declaration of Kathleen Danenberg, and as provided in the specification of the present invention, it is important to be able to detect patients with very low DPD levels undergoing 5-FU based therapy due to the potential of life-threatening toxicity. Thus, as illustrated by the data in the Declaration, the oligonucleotide primers of the present

invention are the most effective at detection of low levels of DPD in various tissue samples and provide an needed improvement over other DPD primers.

Therefore, Applicants respectfully disagree as Gonzalez does not teach each and every element of the claimed invention and Willhauck and Stanta do not make up for these deficiencies. The fact that Gonzalez teaches a method of freezing or fixing a sample for detection is irrelevant, as the present claims involve fixing a portion of a tumor sample in paraffin. Gonzalez does not teach or suggest this. The present claims involve isolating mRNA from the fixed and paraffin embedded (FPE) tumor tissue. Gonzalez does not teach or suggest this. The present claims involve amplifying mRNA from the FPE tumor tissue. Gonzalez does not teach or suggest this. The present claims also involve comparing expression levels of DPD in the amplified mRNA from the FPE tumor sample with the mRNA from an internal control gene. Gonzalez does not teach or suggest this. The present claims also involve the use of claimed primers for amplifying the mRNA. Gonzalez does not teach the claimed primers, regardless of the homology of those primers identified in Gonzalez. Willhauck does not teach or suggest these missing elements and does not make up for the shortcomings of Gonzalez. For example, the Examiner cites Willhauck for teaching comparing the amount of the target gene to an internal gene, including B-actin. Willhauck, however, actually teaches away from the use of housekeeping genes, such as GAPDH and B-actin. (See page 656 column 1). Specifically, Willhauck states that such housekeeping genes are "not suitable for reliable detection of tumor targets with low mRNA expression levels." Thus, applicants respectfully assert that the combination of Gonzalez and Willhauck does not teach nor suggest the claimed invention and therefore does not render the claims obvious.

In response to the Examiner's assertion that it would be obvious to one skilled in the art to combine the teaching of Gonzalez with Willhauck and Stanta, as addressed above, the applications respectfully disagree. Applicants argue that as with Willhauck, Stanta actually teaches away from the claimed invention and, thus, one would not be motivated to combine the teachings of Gonzalez with the teachings of Stanta to arrive at the presently claimed invention. For example, the Examiner cites Stanta for teaching a chaotropic agent, yet Stanta, on page 307 column 1, characterizes the second step of the method as teaching "a proteolysis step with a high concentration of proteinase K in the presence of 1 M guanidinium thiocyanate" to allow for efficient RNA extraction without further degradation. In contrast, the claimed method uses a chaotropic agent (without a high concentration of proteinase K) at higher temperatures for shorter times to extract mRNA from fixed paraffin embedded samples. Further, unlike the assertion that "six hours" is "about" 120 minutes is nonsensical. Additionally, the allegation that

45° C was "about 50 to about 120 °C" or "about 75 to about 120 °C" is also not accurate. Based upon the fragility of RNA, one skilled in the art at the time of the invention would not consider an increase in the temperature or the dramatic increase in time of incubation during RNA extraction as "routine optimizable variations" as the Examiner alleges. Rather, Applicants argue that one of the fundamental inventive concepts of the Applicants patent application is the very idea that by raising the temperature, the RNA would not be destroyed and one could obtain a better yield of RNA from FPE tissue samples. Thus, applicants respectfully assert that the combination of Gonzalez and Stanta does not teach nor suggest the claimed invention and therefore does not render the claims obvious. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

## CONCLUSION

It is believed that the present claims are in conditions for allowance and earnestly request allowance. Extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefore (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 11-0600. The Office is hereby authorized to charge any additional fees or credit any overpayments under 37 C.F.R. § 1.16 or 1.17 to Kenyon & Kenyon Deposit Account No. 11-0600. The Examiner is invited to contact the undersigned at 202-220-4258 to discuss any matter concerning this application.

Respectfully submitted,
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